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PROTON THERAPY SPECIAL FEATURE: REVIEW ARTICLE

Proton therapy for brain tumours in the area of evidence-based medicine

^{1,2,3}DAMIEN C WEBER, MD, ¹PEI S LIM, MD, ¹SEBASTIEN TRAN, MD, ¹MARC WALSER, MD, ¹ALESSANDRA BOLSI, PhD, ¹ULRIKE KIEBSCH, PhD, ¹JÜRGEN BEER, MD, ¹BARBARA BACHTIARY, MD, ^{1,4}TONY LOMAX, PhD and ¹ALESSIA PICA, MD

¹Center for Proton Therapy, Paul Scherrer Institute, Villigen, Switzerland

²University of Bern, Bern, Switzerland

³University of Zürich, Zürich, Switzerland

⁴Department of Physics, ETH, Zürich, Switzerland

Address correspondence to: Damien C Weber

E-mail: damien.weber@psi.ch

Proton therapy (PT) has been administered for many years to a number of cancers, including brain tumours. Due to their remarkable physical properties, delivering their radiation to a very precise brain volume with no exit dose, protons are particularly appropriate for these tumours. The decrease of the brain integral dose may translate with a diminution of neuro-cognitive toxicity and increase of quality of life, particularly so in children. The brain tumour patient's access to PT will be substantially increased in the future, with many new facilities being planned or currently constructed in Europe, Asia and the United States. Although approximately 150'000 patients have been treated with PT, no level I evidence has been demonstrated for this treatment. As such, it is this necessary to generate high-quality data and some new prospective trials will include protons or will be activated to compare photons to protons in a ran-

omized design. PT comes however with an additional cost factor that may contribute to the ever-growing health's expenditure allocated to cancer management. These additional costs and financial toxicity will have to be analysed in the light of a more conformal radiation delivery, non-target brain irradiation and lack of potential for dose escalation when compared to photons. The latter is due to the radiosensitivity of organs at risk in vicinity of the brain tumour, that photons cannot spare optimally. Consequentially, radiation-induced toxicities and tumour recurrences, which are cost-intensive, may decrease with PT resulting in an optimized photon/proton financial ratio in the end.

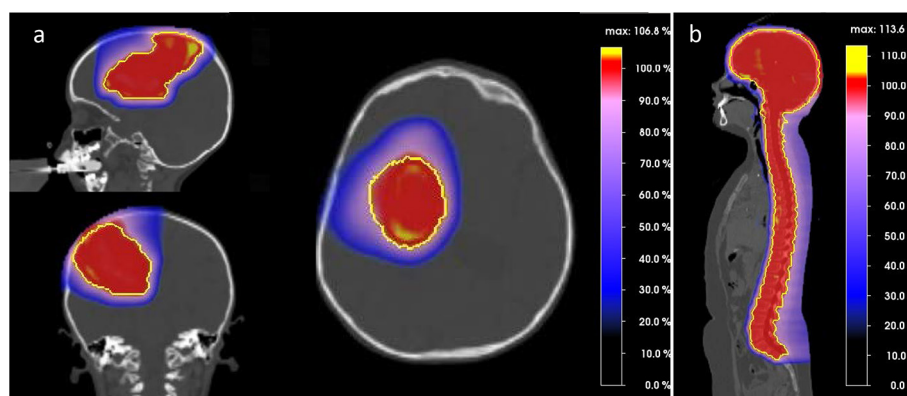
Advances in knowledge: This review details the indication of brain tumors for proton therapy and give a list of the open prospective trials for these challenging tumors.

INTRODUCTION

Radiotherapy (RT) is an important treatment modality in the management of Central Nervous System (CNS) tumours for the optimization of tumour local control. Unlike other non-CNS malignancies, brain tumours have rarely a propensity for distant non-CNS metastases and consequently local control is key for the cure of these challenging malignancies. Recent advances in radiation techniques include the use of intensity- (IMRT) or volumetric- modulated radiotherapy/arc therapy (VMAT), stereotactic radiosurgery/fractionated RT (SRS/SFRT) and particle therapy (mostly protons and carbon ions). As a result of optimal dose conformation provided by the latter modality, particles can be used in a dose-escalation paradigm and/or for dose sparing of critical structures/organs at risks. The former could be applied to radio-resistant CNS tumours,¹ such as skull base chordoma and chondrosarcoma, or

non-benign meningiomas² and the latter in patients with a favorable prognosis, such as those with benign/low-grade brain tumours. For children, RT has been associated with a number of acute and late adverse events detailed later in this paper. Protons may decrease the rate of acute³ and, more importantly, late toxicity⁴ usually seen with photon therapy and would thus increase substantially the therapeutic ratio of RT. The present paper details the most recent data for proton therapy delivered to patients with CNS tumours. Noteworthy, no data regarding carbon ions for CNS malignancies will be summarized in this manuscript and we have included skull base tumors in this brain tumor review, as it is a major indication for protons. First, this paper will detail the rational of using protons for treating brain tumors. Second, an overview of the existing trials will be described and an attempt to discuss the limitations of such studies will be made. A summary of existing data for CNS tumours

Figure 1. Sagittal, axial and coronal views of proton dose distribution for a parieto-frontal tumor. PTV is shown in yellow. Figure 1b. Sagittal view of proton dose distribution for craniospinal irradiation. PTV is shown in yellow. Noteworthy, the color wash dose level display all dose levels. As such, absence of colors equals to absence of dose.



in adults and children alike will be provided and each section will finish with statements pertaining to the informed analysis. Finally, the additional costs and potential financial toxicity for patients of protons will be discussed at the end of this paper.

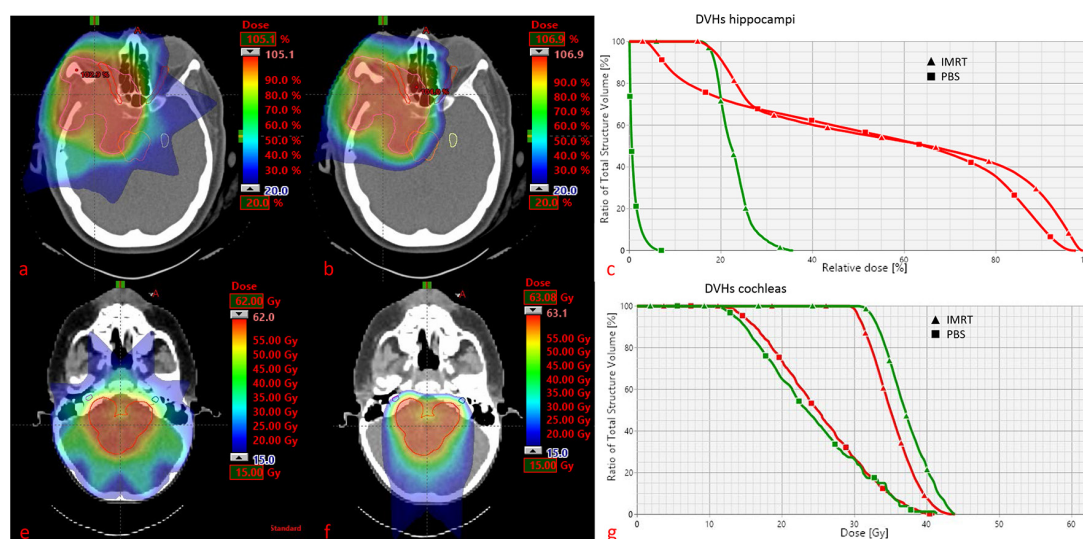
Proton beam therapy for brain tumours

This section elaborates on the physical rationale and dosimetric evidence for PT. Dose distribution in PT is characterized by a well-defined maximum range, which is a function of the initial energy, and a sharply defined Bragg Peak, where the bulk of the dose is deposited.⁵ Beyond the Bragg Peak, the dose drops to zero within a few millimetres. Compared to photons, this dose deposition results in a superior dose conformity and lower total integral dose delivered to surrounding tissue. This remarkable dose-profile is even more pronounced for Intensity Modulated PT (IMPT) available for Pencil Beam Scanning (PBS) systems,

which can achieve particularly steep dose gradients.⁶ CNS tumours are inevitable in vicinity to many critical organs at risk (OARs),⁷ making them an especially relevant indication for PT. This rationale is supported by clear evidence for a dose-response relationship for many radiation-induced toxicities seen after RT for brain tumours. As an example, dose to the hypothalamus and pituitary correlates with the degree of endocrine dysfunction,⁸ and dose to the hippocampus correlates with memory outcomes.⁹

The dosimetric advantage of PT compared to photons is undisputed, but the magnitude of clinical benefit is unknown. This benefit may substantially differ from individual cases to cases and is to a large degree dependent on tumor location. Adeberg *et al*¹⁰ evaluated the relative benefit of protons for five typical brain tumor locations and suggested that in general parietal tumours seem to benefit the most in terms of brain sparing. An exemplary

Figure 2. Supratentorial meningioma case. Doses as % of the prescribed dose and minimum dose level set at 20%. (a) IMRT dose distribution; (b) PBS dose distribution; (c) DVHs for homolateral (red) and contralateral (green) hippocampus. VOIs represented are PTV, brainstem, optic nerves and contralateral hippocampus. Infratentorial ependymoma case. Doses as absolute (GyRBE), minimum dose level set at 15GyRBE. (e) IMRT dose distribution; (f) PBS dose distribution; (g) DVHs for both cochleas (red and green). VOIs represented are PTV and both cochleas.



PT dose distribution for a parieto-frontal located brain tumor is shown in Figure 1a. Even for very complex target volumes (Figure 2) involving large parts of the brain, such in whole-ventricular RT for intracranial germ cell tumours, a dosimetric comparison study showed an approximately one-third reduction in integral dose to the brain, and also a better sparing of the circle of Willis with PT.¹¹ This may be clinically significant, as radiation dose delivered to the circle of Willis was recently proposed as the best predictor of stroke in childhood brain cancer survivors.¹² Moreover the dosimetric advantage is particularly striking for large target volumes, such in the case of craniospinal irradiation (CSI), where PT is able to completely spare OARs anterior to the vertebrae, as it is demonstrated in Figure 1b. Compared with modern photon techniques, PT obtained the lowest mean doses for OARs in CSI, with dose reductions of >10.0 Gy for parotid glands, thyroid and pancreas.¹³ Figure 2 details the decrease of dose delivered with PT as opposed to IMRT to the hippocampus and cochleas for a supra- and infratentorial tumor, respectively. Tamura et al¹⁴ estimated by *in silico* modelling that the use of PT instead of photons may result in a decrease in the lifetime attributable risk of radiation-induced secondary cancer after CSI. Although these results of *in silico* modelling have been confirmed by a previous study,¹⁵ caution should be taken not to over interpret these data stemming from a modelling computational paradigm, which do not represent 'real-life' data. Preliminary evidence suggests that this PT dosimetric gain also translates into a clinical benefit such as, for example, reduced neuro-cognitive disability¹⁶ and improved quality of life.¹⁷

The superior dose conformality of PT (Figure 2) has also however its dose-delivery hazards, in terms of increased sensitivity to range and setup uncertainties, particularly so for IMPT. Robust planning¹⁸ and robust optimization¹⁹ can help to mitigate these dosimetric uncertainties. Another concern is the clinical use of a constant value of 1.1 for the relative biological effectiveness (RBE) for PT planning, whereas it is well known that RBE increases with increasing linear energy transfer (LET), thus presenting the highest value in the distal fall-off.²⁰ Other factors, not limited but including total dose, fractional dose, biological endpoint, oxygenation and tissue or cell type (characterized normally by α/β) have an influence on RBE.^{20,21} LET/RBE evaluation and LET optimization of PT plans can avoid high LET areas, and therefore unintended increase in biological dose, in critical structures such as the brainstem²² or periventricular area²³ where the brain stem-cells are located. There is a concern within the community that high-LET values at the distal range of the beam may cause toxicities be it radiological²⁴ or clinical.²⁵ For example, adjusting treatment field angles for posterior fossa tumours can substantially reduce LET values in this OAR.²⁶ Future developments in these and other areas are likely to only enhance the benefits of PT even further.

Establishing the role of proton therapy for the management of brain tumours: clinical trials

In the era of evidence-base medicine (EBM), high quality of data²⁷ is needed to justify the additional cost factor associated with proton therapy for brain and non-CNS tumours alike. Although some authors have challenged the hierarchal evidence

paradigm in EBM,²⁸ it remains that randomised controlled trials (RCTs), representing the so-called level I evidence, are of paramount importance in the assessment of the 'value' of any treatment modality in cancer care. The ethical issues of such RCTs for proton therapy have been long debated and are not the focus of this section.²⁹ Clinical validation of proton therapy can also be achieved with a non-RCT paradigm: specifically, a model-based driven validation approach, with an enrichment of the experimental arm.³⁰ It is foreseeable that a combination of these trial strategies will best generate data that will create scientifically sound evidence on how best to select patients for protons and increase the therapeutic balance of a number of malignancies, including CNS tumours for value-based cancer management. Caution however should be stressed that, depending on the selected study endpoint, such as late toxicity including but not limited to radiation-induced tumours, the event can be observed after a long interval after PT. As such, the follow-up time of studies should be consequentially sufficient, which creates a significant challenges for prospective trials, one of which is the trial funding that should be appropriate to fund an extended period of follow-up.

A number of RCTs and prospective Phase II trials have been proposed and are currently accruing patients worldwide. Exclusion criteria of the majority of trials are previous radiation to the head and neck or brain and very extensive lesions, which would have been previously defined as gliomatosis cerebri. Several databases were queried (clinicaltrials.gov, CTSU/NRG, EORTC, PTCOG) and 43 prospective brain tumour trials activated between 1996 and 2019 were identified. Trials that assessed the value of targeted agent/immune checkpoint inhibitors or hypoxic target agents with RT including protons were excluded. Median accrual target of these trials was 80 patients, ranging from 12 to 625. Only a minority ($n = 3$; 7%) of trials had no age limit. Most trials were for adults ($n = 23$; 53%) or pediatric ($n = 12$; 30%) patients. Three (7%) studies were for children and adolescent and young adults. Interestingly, a substantial number of studies ($n = 9$; 21%) were for all brain tumours. The most common brain tumours for these trials were chordoma or chondrosarcoma ($n = 7$; 16%), meningioma ($n = 6$; 14%) and low-grade glioma ($n = 6$; 14%). Most of the studies were however not accruing ($n = 17$; 39%) or were in the process of activation ($n = 2$; 5%). Five (12%) studies were closed and 3 (7%) had an unknown status. The 16 (37%) remaining studies accruing patients in Europe and in the United States are detailed in Table 1. One of the low-grade glioma trials has been recently closed, achieving target-accrual. Noteworthy, WHO grade II glioma patients could be included in this trial from Boston, providing that progressive/recurrent disease was observed, neurological symptoms were uncontrolled and/or patient was aged >40 years or presented MIB-1 of $\geq 3\%$. Mean age of this cohort was 37.5 years (range, 22–56) and the gender male/female ratio was 1.9. 40% of the cohort have been followed at 5 year. The results will be published soon.

Table 1 displays also a number of tumour registries that are active in the United States, one of which is dedicated to children only. The target of total number of patient's registration is over 28'000. In Europe, it is also foreseen to have a prospective data collection

Table 1. Prospective trials and tumor registries currently accruing patients in Europe and in the United States for brain tumours

Tum ^o r type	NCT number	All ^o cation	Activati ^o n (cl ^o sed) [year]	# of patients	Age limit	Hyp ^o thesis	Primary endp ^o int	T ^o tal dose (d ^o se per fx) [GyRBE]	status
Europe (lead)									
All brain tum ^o rs (Dresden, D)	02824731	N ^o n-randomized Phase II	1997	418	n ^o	rate of chronic 1 year toxicity: 15% lower with protons	Ch ^o nic toxicity @ 1 year and QoL	54-60(27-30)	accruing
WH ^o grade II/WHO grade III and IDH mutated (Essert, D)	DRKS 00015160 N ^o A-25	pr ^o spective, randomized (Ph ^o tons vs Protons)	2019	80	≥18 years	Less impairment of neurocognition after proton therapy when compared to photon radiotherapy	Neur ^o cognition after 3 years	WH ^o II: 54 Gy (30 × 1,8 Gy) WH ^o III: 60 Gy (30 × 2 Gy) O ^o r 59,4 Gy (33 × 1,8 Gy)	accruing
United States (lead)									
All brain tum ^o rs Washington Uni. School of Medicine	02559752	N ^o n-randomized Phase II	2015	80	4–21 years	Testing as measured by an acceptance rate of 60% of eligible patients administered PT	Feasibility of obtaining serial computer-based neurocognitive testing for patients administered PT	NR	accruing
Craniopharyngioma St Jude's Children H ^o spital	02792582	N ^o n-randomized Phase II	1996	140	≤21 years	Increase of PFS @ 3 years compared to photon data	PFS @ 3 years	54 (1.8)	accruing
Meningi ^o ma (Recurrent) Washington Uni. School of Medicine	03267836	Phase Ib	2018	12	≥18 years	Proof of concept to demonstrate on-target effect of the PT-ICI	Immunogenicity as measured by changes of CD8+/CD4 + TILs	20(5) with concomitant Avelumab	accruing
Meningi ^o ma (non-benign) Mass. General H ^o spital	02693990	N ^o n-randomized Phase I/II	2016	60	≥18 years	D ^o se escalation	Assess Safety and Utility of Increased Dose IMPT (DLT)	D ^o se escalation 3 × 3 design	accruing
L ^o w-grade brain tumours Mass. General H ^o spital	03286335	Observational study	2018	100	≥18 years	N ^o ne (observational)	Tum ^o r control @ 2 years	NR	accruing
Vestibular Schwann ^o ma Mass. General H ^o spital	01199978	Observational study	2010	30	≥18 years	N ^o ne (observational)	Incidence of late toxicity @ 2 year	54(27)	Accruing

(Continued)

Table 1 (Continued)

Tumour type	NCT number	Allocation	Activation (closed) [year]	# of patients	Age limit	Hypothesis	Primary endpoint	Total dose (dose per fraction) [GyRBE]	status
All brain tumours requiring CSA <i>Mass: General Hospital</i>	03281889	Feasibility	2018	20	3–18 years	T ₀ assess if IMPT is feasible for CSA vertebral body sparing	Rate of G3/4 haematological toxicity < 5% within 3 months	NR	Accruing
Recurrent Ependymoma <i>St Jude's Children's Hospital</i>	02125786	N ⁿ -Randomised Phase II	2014	99	1–21 years	T ₀ assess if surgery and fractionated re-irradiation with either proton or photon is effective and safe	PFS and OS @ 3 years	NR	Accruing
Glioblastoma <i>NRG Oncology</i>	02179086	Randomised Phase II	2014	606	≥18 years	D ₀ se escalation with IMRT or PT is better than standard dose photon radiation therapy	OS dose escalation vs standard dose	NR	Accruing
IDH mutant Glioma (GII/III) <i>NRG Oncology</i>	03180502	Randomised Phase II	2017	120	≥18 years	PT will preserve cognition compared with IMRT	Change in cognition (CTB COMP score) up to 10 years	NR	Accruing
Medulloblastoma <i>St Jude's Children's Hospital</i>	01878617	Phase II	2013	625	3–39 years	Assess clinical and molecular risk directed therapy	PFS @ 2 years, neurocognition @ baseline and 12 weeks	NR	Accruing
Brain tumours <i>Mayo</i>	03055364	Observational study	2017	160	≥4 years	N ⁿ e (observational)	Cognitive performance change (CogState) within 12 months of radiotherapy	NR	Accruing
Meningioma (G II) <i>NRG Oncology</i>	03180268	Randomised Phase III	2017	148	≥18 years	Observation vs adjuvant RT in the completely resected setting	PFS up to 10 years	59.4 (1.8)	Accruing
Leptomeningeal metastases <i>MSKCC</i>	03520504	Phase I	2018	26	≥10 years	Identification of safe and effective dose for PT in leptomeningeal metastases	Number of patients with DLT	30 (3) 25 (2.5) CSA	Accruing
Patient Registries									

(Continued)

Table 1 (Continued)

Tumour type	NCT number	All ^o cation	Activati ^o n (cl ^o sed) [year]	# of patients	Age limit	Hyp ^o thesis	Primary endp ^o int	T ^o tal dose (d ^o se per fx) [GyRBE]	status
All tumours Washington U	02040467	Observational (patient registry)	2013	3200	n ^o	N ^o ne (observational)	All treatment data	NR	Accruing
All Paediatric tumours Paediatric Consortium Registry (PCCR)	01696721	Observational (national patient registry)	2012	5000	≤21 years	N ^o ne (observational)	Establish registry	NR	Accruing
All tumours Proton Collaborative Group	01255748	Observational (patient registry)	2010	20,000	All	N ^o ne (observational)	Establish registry and track outcomes	NR	Accruing

CSA, Craniospinal axis; DLT, dose-limiting toxicity; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon radiotherapy; NCT: NCI/Clinical Trials; NR, not reported; OS, Overall Survival; PFS, progression-free survival; QoL, quality of life; RT, radiotherapy; TIL, tumour infiltrating lymphocytes; fx, proton therapy dose per fraction.

^aUpfront radiotherapy or re-irradiation 30 Gy/RBE in 5 Gy RBE per fraction or 36 Gy/RBE in 2 Gy RBE per fraction.

^bClinical Trial Battery Composite score (calculated from the Hopkins Verbal Learning Test Revised [HVLTR]) Total Recall, HVLTR Delayed Recognition, Controlled Oral Word Association (COWA) test, Trail Making Test (TMT) part A and part B.

of patients treated with protons in the framework of PARTICLE-Care. This project is a joint collaboration of the European Organisation for the Research and Treatment of Cancer (protocol: E²RADlatE, EORTC 1811) and the European Society for Radiotherapy and Oncology. It is foreseen that the first patient will be included into this prospective database by the end of 2019.

Adult brain tumours

Patient with benign brain tumours and low-grade CNS tumours might show some clinical benefit from PT. A substantial number of Low Grade Glioma (LGG) patients are long-term survivors.³¹ The negative impact of photon radiation therapy on cognition has been demonstrated.³² Plan comparative studies have shown the potential of proton therapy to decrease radiation dose delivered to OARs.³³ Currently, there are no published data of randomized trials comparing protons with photons for these tumours (Table 1). Reported results however regarding long-term toxicities from clinical proton studies show encouraging results,^{34–36} although the patient numbers are small. More elucidation on the real benefit regarding the use of protons in treating LGGs can be expected from the results from the ongoing randomized trial.

Due to the poor prognosis of high-grade gliomas, a dose escalation paradigm has been advocated for these challenging tumours. A study applying an escalated boost with protons to a total dose up to 90 Gy(RBE) lead to improvement in tumor control rate as well as median survival time.³⁷ Nevertheless, the study enclosed only a small number of patients with no molecular analysis and a substantial number of patients had to undergo surgery due to radiation brain necrosis.

Some of the meningiomas can also be considered low-grade benign tumours. Total surgical resection is the treatment of choice for symptomatic/progressive meningioma. However, not all meningioma are suitable for surgery and therefore radiation therapy is often indicated. In particular, patients with residual non-benign, recurrent or high-grade tumours are candidates for radiation therapy. Large and complex shaped meningioma located close to brainstem (Figure 2), optical nerve, pituitary gland and cochlea may present however a therapeutic challenge and proton may provide dose escalation possibilities for non-benign meningiomas.² Eight retrospective studies delivering PT were conducted across a number of countries including Switzerland, Germany, Sweden and USA.^{38–45} The sample size within the studies ranged from 39 to 170 participants (Table 2). Four studies included meningioma Grad 1–3,^{40,42,44,45} while two included Grade 1–2^{39,41} and one Grade one meningioma only.⁴³ In two studies a combination of photons and carbon ions was given to patients with Grade 2–3 meningioma whereas patients with Grad one tumours received proton therapy only.^{42,45} Five-year local control rates for low-risk meningioma were better (94–100%) when compared with high-risk meningioma (49–88%) and tumor grading was found to be of prognostic significance in univariate analysis in four studies.^{39,40,44,45} Proton therapy induced toxicity was moderate with a rate of 3.6–12.8% Grade ≥ 3 late effects. The results stemming from these small PT series are in line with modern photon series and cannot prove that proton are superior to conventional radiotherapy.

Table 2. Recent proton therapy studies for meningioma in adult patients

Author [ref]	year	Tumor type	# patients	Median Dose (GyRBE) (Range)	Median FU (months) (range)	Proton Therapy only	PBS only	Outcome	Positive prognostic factors [Univariate analysis]	Toxicity
Halasz et al. ³⁹	2011	Meningioma WHO Grade 1–2	<i>n</i> = 50 Grade 1: <i>n</i> = 12 (24%) Grade 2: <i>n</i> = 6 (12%) Grade not known: <i>n</i> = 32 (64%)	13 (10–15.5) in one fraction	32 (6–133)	yes	Scattering (stereotactic)	3y-LC: 94%	WHO Grade one vs atypical histology (<i>p</i> = 0.03) Recurrent vs non-recurrent meningioma (<i>p</i> = 0.006)	Acute Transient facial pain 4% Late Seizures associated with cerebral edema 12% Panhypopituitarism 2%
Weber et al. ⁴⁰	2012	Meningioma WHO Grade 1–3	<i>n</i> = 39 (three re-irradiation)	Grade 1–2: 52.2–56 Grade 3: 60.8 (±5.3)	54.8 (6.2–146.8)	yes	yes	5y-LC: Grade 1: 100% Grade 2–3: 49.1%	WHO Grade 1 vs 2/3 (<i>p</i> = 0.001) GTV < 21.5 vs. >= 21.5 ml (<i>p</i> = 0.03)	CTCA Acute: Grade 2: 12.5% Grade 3: 0% Late: Grade ≥ 3: 12.8%
Slater et al. ⁴¹	2012	Meningioma Grade 1–2	Entire cohort <i>n</i> = 72 Grade 1: <i>n</i> = 47 (65%) Grade 2: <i>n</i> = 4 (6%) Grade not known: 21 (29%)	Grade 1: 50.4–66.6 Grade 2: 54–70.2	74 (3–183)	yes	Scattering	5y-LC Overall: 96% Grade 1: 99% Grade 2: 50% 5y-OS 99% (disease-specific)	No significant differences for tumor size (GTV), dose, number of surgeries and WHO Grad	optic neurologic symptoms: 4.2% brain edema: 2.8% Transient diplopia 1.4% Panhypopituitarism 4.2%
Combs et al. ⁴²	2013	Meningioma WHO Grade 1–3	Entire cohort <i>n</i> = 107 WHO Grade 1: 71 (66%) WHO Grad 2/3: <i>n</i> = 36 (34%)	Grade 1: 57.6 Grade 2/3: N.R.	12 (2–39)	Grade 1: PT only Grade 2/3: photons/carbon ion boost	Grade 1. Yes Grade 2/3: combination of photon/carbon	2y-LC: Grade 1: 100% Grade 2/3: 33%	N.R.	N.R.
McDonald et al. ³⁸	2015	Meningioma WHO Grade 2	<i>n</i> = 22	63 (54–68.4)	39 (7–104)	yes	N.R.	5y-LC: 71.1%	Dose > 60 Gy vs ≤60 Gy (RBE) (<i>p</i> = 0.038)	Acute ≥Grade III: 0% Late ≥Grade III: one pt.

(Continued)

Table 2 (Continued)

Author [ref]	year	Tumor type	# patients	Median Dose (GyRBE) (Range)	Median FU (months) (range)	Proton Therapy only	PBS only	Outcome	Positive prognostic factors [Univariate analysis]	Toxicity
Vlachogiannis et al. ⁴³	2017	Meningioma WHO Grade 1	<i>n</i> = 170	21.9 (14–46) 2–6 Gy/fx	84 (range N.R)	yes	Scattering (stereotactic)	5y-PFS: 93% 10y-PFS: 85%	Multivariate analysis: Age: <i>p</i> = 0.009 Localization: middle fossa <i>p</i> = 0.04	Pituitary insufficiency: 3.5% Radiation necrosis: 2.9% Visual impairment: 2.9% Expansive tumour cyst: 0.5%
Murray et al. ⁴⁴	2018	Meningioma WHO Grad 1–3	Entire cohort: <i>n</i> = 96 Grade 1: <i>n</i> = 61 (63%) Grade 2: <i>n</i> = 33 (34.1%) Grade 3: 2 (2.1%)	Grade I: 54 (50.4–64) Grade II and II: 62 (54–68)	56.9 (range, 12–207)	Yes	Yes	5y-LC: Entire cohort: 86.4% Grade 1: 95.7% Grade 2/3: 68% 5y-OS: entire cohort: 88.2% Grade 1: 92.1% Grad 2/3: 80.7%	5y-LC WHO Grade 1 vs 2/3 (<i>p</i> < .001) Timing of PT: Initial vs recurrent (<i>p</i> = .006) Tumor site: Skull base vs non-skull base (<i>p</i> = 0.014) Gender: Female vs Male (<i>p</i> = 0.32) 5y-OS	CTCA Acute ≥Grade III: 0.96% Late ≥Grade III overall: 10% optic toxicity: 6.7% brain edema: 0.96% brain necrosis: 1.9%
El Shafie et al. ⁴⁵	2018	Meningioma WHO Grade 1–3	Entire cohort: <i>n</i> = 110 Grade 1: 60 Grade 2: 7 Grade 3: 1 not known: 42	Protons: 54 (50–60); 1.8–2.0/fx Carbon ion: 18; 3.0/fx	46.8 (95%CI: 39.9–53.7)	Proton: <i>n</i> = 104 Photons/Carbon ion: <i>n</i> = 6	Yes Grade 2/3: combination of photon/carbon	5y-PFS: Entire cohort: 96.6% Low risk: 96.6% High risk: 75% 5y-OS: 96.2 %	Histology: low vs high risk: <i>p</i> = 0.02	CTCAE Acute: Grade III: 1.8% (mucositis, nausea) Late: Grade III: 3.6% (hypopituitarism, radionecrosis)

FU, follow-up; LC, local control; NR, not reported; OS, overall survival; PBT, proton beam therapy; PFS, progression free survival; fx, fraction.

Table 3. Recent proton therapy studies for skull-base tumors (chordoma and chondrosarcoma) in adult patients

Author [ref]	year	Tumor type	^a patients	Mean Dose (GyRBE) (Range)	Mean FU (months)	Proton Therapy only	PBS only	Outcome	Positive prognostic factors LC ($p < 0.05$) [Univariate analysis]
Youn et al. ⁶¹	2018	chordoma	34	69.6	42.8	yes	yes	5yLC: 87.3% ^b 5yOS: 92.9% ^b	Skull-base vs cervical
Fung et al. ⁵³ c	2018	chordoma	106	(68.4–73.8)	61.0	no	no	5yLC: 88.6%	Tumor volume < 25 cc
Weber et al. ⁵¹ c	2018	ChSa	251	70.2	88.0	no	no	5yLC: 93.1% 5yOS: 93.6%	Tumor volume < 25 cc Non-OA compression
Takagi et al. ⁵⁴	2018	chordoma	11	65.0/20 fx	71.5	yes		5yLC: 85.0% ^b 5yOS: 86% ^b	Surgery before PT ^b
Demizu et al. ⁶⁴	2017	Chordoma & ChSa	68	70	52.6	yes	yes	5yLC: 71.1% 5yOS: 75.3%	Female gender
Weber et al. ⁵¹	2016	Chordoma & ChSa	222	72.5	50.0	yes	yes	7yLC: 70.9% 7yLC: 93.6% ^d 7yOS: 81.7% ^b	Non-compression BS GTV ChSa vs chordoma
Hayashi et al. ⁶²	2016	chordoma	19	77.4–78.4 ^a	61.7	yes	yes	5yLC: 75.0% 5yOS: 83.2%	NR
Feuvret et al. ⁶⁵ c	2016	ChSa	159	70.2	77.0	no	no	5yLC: 96.4% 5yOS: 94.9%	Age < 40 years ^e primary disease status ^e
Deraniyagala et al. ⁶⁶	2014	chordoma	33	(77.4–79.4)	21.0	yes	no	2yLC: 86.0% 2yOS: 92.0%	NR
Yasuda et al. ⁶⁷ c	2012	chordoma	17	68.9	46.1	no	no	5yLC: 70.0% ^b 5yOS: 83.4% ^b	≥47 years Skull-base vs CCJ
Fuji et al. ⁶⁸	2011	Chordoma & ChSa	16	63.0	42.0	yes	yes	3yLC: 86.0% (chordoma) 3yOS: 100.0% (chordoma) 3yLC: 100.0% (ChSa) 3yOS: 100.0% (ChSa)	NR
Noel et al. ⁶⁹	2001	Chordoma & ChSa	45	67.0	30.5	no	no	3yLC: 83.1% (chordoma) 3yOS: 91.0% (chordoma) 3yLC: 90.0% (ChSa) 3yOS: 90.0% (ChSa)	<55 years Tumor volume < 29 cc
Hug et al. ⁵²	1999	Chordoma & ChSa	58	70.7	33.0	yes	no	5yLC: 54.0% (chordoma) 5yOS: 88.0% (ChSa)	Tumor volume < 25 cc Non-compression BS
Terahara et al. ⁷⁰ c	1999	Chordoma	115	68.9	NR	no	no	5yLC: 79.0% (chordoma) 5yOS: 59.0% (chordoma) 5yLC: 94.0% (ChSa) 5yOS: NR (ChSa)	Male gender Minimum dose Target dose EUD

(Continued)

Table 3 (Continued)

Author [ref]	year	Tumor type	^a patients	Mean Dose (GyRBE) (Range)	Mean FU (months)	Proton Therapy only	PBS only	Outcome	Positive prognostic factors LC ($p < 0.05$) [Univariate analysis]
Munzenrider et al. ⁷¹	1999	Chordoma & ChSa	621	(66.0–83.0)	41 ^d	no	no	10LC: 54.0% (chordoma) 10OS: 54.0% (chordoma) 10yLC: 88.0% (ChSa) 10yOS: 90.0% (ChSa)	Male gender Tumor volume < 70 cc
Austin-Seymour et al. ⁷²	1989	ChSa	68	69.0	41	no	no	5yLC: 82% 5yDFS: 76%	NR
Berson et al. ⁷³	1988	Chordoma & ChSa	45	(59.4–80.0)	33pts > 1 year	no	no	5yLC: 59.0% ^b 5yOS: 62.0% ^b	ChSa Tumor volume < 20 cc Non-recurrent tumour

LC, local control; OS, overall survival; ChSa, chondrosarcoma; BS, brainstem; GTV, Gross tumor volume; CCJ, cranio-cervical junction; EUD, equivalent uniform dose; PT, proton therapy; fx, fraction; NR, not reported; OA, optic apparatus; pts, patients; FU, follow-up.

^aHyperfractionated proton therapy

^bEntire cohort, including skull base and extra cranial tumours

^cPartial publication of cohort outcome in another paper

^dChondrosarcoma only

^eFor Progression-free survival

^fMedian value

In summary, it is unlikely that proton therapy delivered for high-grade brain tumors might translate into a substantial clinical benefit for CNS-tumor patients. Protons could however be administered to low-grade (*i.e.* glioma) or benign (*i.e.* meningioma) brain tumors, as these patients experience substantial long survival times, in order to possibly decrease the probability of long term toxicity. Alternatively, proton therapy could be administered to patients with non-benign meningioma with a dose-escalation paradigm.

SKULL-BASE TUMOURS

Skull-base chondrosarcoma (sbChS) and chordoma (sbC) are very rare tumours with an incidence of <1 per million.⁴⁶ They are usually in direct vicinity of OARs, including but not limited to the optic apparatus, brainstem, pituitary gland and cochleae and are considered radio-resistant.^{47,48} Local tumour control is associated with overall survival and is thus of paramount importance.^{49,50} SbChS and sbC are usually managed with cytoreductive surgery and postoperative radiotherapy. The importance of optimal surgery (*i.e.* optimizing the tumor geometry/debulking) with potentially sequential surgical procedures, before radiotherapy has been advocated by many groups.^{50–54} The outcome of patients with sbChS/sbC treated with adjuvant or salvaged photon radiation therapy is not optimal. When gauging the benefit of protons for these skull-base tumours, it is important to acknowledge that, due to the rarity of this condition, only observational studies stemming usually from one institution, with few exceptions,⁵⁰ have been published. Consequentially, no level I or II evidence have been proven on the superiority of protons over photon radiotherapy, although the outcome data published by non-particle radiotherapy is somewhat poor. Two photon series reporting on 17 and 48 sbC and extra cranial chordomas patients have shown that delivering a median dose of 50 Gy with conventional radiotherapy resulted in a 5 year PFS and 5 year LC of 17 and 23%, respectively.^{55,56} As such, conventional radiotherapy may provide valuable palliation for these challenging patients but chordomas are rarely cured with this therapeutic modality. It has been claimed that historical photon series, such as those reported above, do not reflect the accurate efficiency of modern photon radiotherapy series. A recent study from the UCLA group reported on 57 sbC patients treated with a median dose of 17.8 and 63.4 Gy delivered with SRS and SFRT, respectively.⁵⁷ The observed 5 year PFS for the entire cohort was only 35.2%. Of note, SRS and SFRT produced comparable rates of tumour control. Numerous modern SRS and SFRT series have shown suboptimal outcomes for sbC patients treated with these radiation modalities.^{57–59} These suboptimal results may be best explained by the stereotactic margins defined during the planning process and radiation dose delivered to these patients. Regarding the former, Snider et al have shown undisputedly the importance of margins for extracranial chordomas.⁶⁰ The seminal paper by Pearlman et al have shown a dose-response for chordomas.⁴⁷ More recently, a South Korean study reported on 35 sbC patients treated with a median 75.5 EQD2 delivered by proton therapy. The observed 5 year local tumour control was 92.8 and 63.0% for patients treated with ≥ 69.6 and <69.6 Gy, respectively.⁶¹ Likewise, an analysis of 863 chordoma patients captured in the National Cancer Data base has shown undisputedly that dose for chordoma was

associated with a significant increase in OS on univariate analysis.¹ Other proton series have shown such a dose-response with sbC.⁶² This dose-response relationship has also been observed with photons^{55,63}: in the above-referred US series, higher dose of SFRT was associated with a significant higher rate ($p = 0.013$) of tumour local control.⁵⁷ As such, high-dose radiation therapy, with non-stereotactic margins, have to be delivered to chordoma patients postoperatively. Table 3 details the outcome and prognostic factors of sbChS and sbC adult patients treated with proton therapy, mostly delivered with a passive scattering paradigm. Noteworthy, the prognostic impact of gender is unproven, as all but two series with contradictory results,^{64,70} have shown that chordoma is gender-neutral. Tumour volume before proton therapy, with various cut-offs ranging from 20 to 70 cc, is a major prognosticator. Interestingly, the outcome of sbC and sbChSa patients have improved substantially in recent years (Table 3). Finally, delivering high dose proton radiation to the skull base tumours may induce toxicity,^{52,65–69,71–74} including but not limited to the brainstem. At the Paul Scherrer Institute, we have seen no brainstem radiation toxicity in adult skull-base tumour patients treated with protons. Debus et al reported on 367 skull base tumours patients treated in Boston with combined proton/photon radiotherapy.⁴⁹ Brainstem toxicity was observed in 4.6% of cases and the estimated toxicity-free survival was 88%.

Protons should thus be the standard of care for sbC or sbChSa, as a dose escalation can be achieved with this treatment modality, maximizing the chances of cure for these challenging patients.

Pediatric brain tumours

Cancer affects more than 380'000 children aged 0–19 every year globally⁷⁵ and is the leading cause of childhood death by disease in high-income countries (HIC). Nevertheless, cancer cure rates in HIC currently are near 80% and are on the rise thanks to new advances in medical treatments. This leaves many childhood cancer survivors (CCS) with a potentially normal lifespan, during which maintaining both good health status and quality of life is of paramount importance.⁷⁶ Treatment-related toxicity brings a significant morbidity burden on CCS, most of all for patients with primary brain cancers.⁷⁷ Reasons for this are an increased sensitivity due to ongoing tissue growth and neuro-cognitive development, smaller anatomic dimensions bringing critical organs closer to treatment areas and a longer lifespan left to develop side-effects. The most significant toxicities associated with brain tumor irradiation are vascular complications such as radiation necrosis (RN) and Moya-Moya syndrome, impairment of neurocognitive development, including loss of IQ scores, visual, hearing or endocrine deficits as well as skin changes such as alopecia. In the case of CSI (Figure 1b), neck, thoracic, abdominal and pelvic organs can develop late sequelae of radiation therapy. As an example, vertebral body irradiation leads to decrease of adult height^{78–80} with a reported incidence rate of 3–26%.⁸¹ RN can result in numerous symptoms or deficits, depending on its location, such as seizures or motor impairment. Seven papers reported on RN induced by proton therapy in pediatric patients (Table 4). Sample sizes ranged between 17 and 313 patients, with ages between 19 months and 10 years. Time to RN ranged between 3 and 9 months. Median PT doses of 54 Gy

Table 4. Literature review of cerebral necrosis for proton therapy

Author [ref]	Year	Tumor type	# pts	Median Age [years]	Median Dose [GyRBE] (range)	Time to RN [months]	Toxicity	Prognostic Factors
Sabin et al. ⁸²	2013	EP, CPC, PNET, MB, ATRT	8/17	2.5	54	3.9	47% pseudoprogression	PT after chemotherapy
Indelicato et al. ⁸³	2014	EP, CFLGG, MB, PNET, PMRh	11/313	5.9	54	3	3.8% Gr < 3@2y 2.1% Gr 3 @2y	Age < 5y; PF; V55Gy; Dmax
McGovern et al. ⁸⁴	2014	ATRT	5/31	19	Local PT 50.4 CSI 54	4	16% @2y Gr1-2	Age < 5y; intensive Cht prior PT
Gunther et al. ⁸⁵	2015	EP	72 16/37 PT 6/35 IMRT	4.4 PT 6.9 IMRT	59.4 PT 54 IMRT	3.8 PT 5.3 IMRT	43% PT 17% IMRT 3PT persistent neurological deficits	PTvsIMRT higher rate of imaging changes Age > 3 y BS
Giantssoudi et al. ⁸⁶	2016	MB	4/111	10.5	54	9	3.6% @5y 2.7% @5y (grade3+)	WPF vs IF
Bojaxhiu et al. ⁸⁷	2018	EP, CFLGG, MB, PNET, other	29/171	3.3	54	5	17% RN; 11% WMLs	Cht, EP, hydrocephalus
Gentile et al. ⁸⁸	2018	MB, EP, ATRT	5/216	6.6	54	8.5	2.0% @5y (grade ≥ 2)	Dmax < 55.8 Gy; V55 ≤ 6%

GyRBE, Gray in relative biological effectiveness; ATRT, atypical teratoid rhabdoid tumor; CF, craniopharyngioma; CPC, choroid plexus carcinoma; CSI, craniospinal irradiation; Cht, chemotherapy; EP, ependymoma; IF, involved field; IMRT, intensity modulated radiation therapy; LGG, low grade glioma; MB, medulloblastoma; PF, posterior fossa; PMRh, parameningeal rhabdomyosarcoma; PNET, primitive neuroectodermal tumor; RN, radiation necrosis; WML, white matter lesion; WPF, whole posterior fossa; pts, patients.

Table 5. Recent proton therapy studies for pediatric brain tumours

Author [ref]	year	Tumor type	# pts	Median Age [years]	Median Dose [GyRBE] (range)	Median FU [months] (range)	Outcome	Late Toxicity
De Amorim Bernstein et al. ⁹⁶	2013	AT/RT	10	2.3	50.4 (50.4–55.8); three pts CSI (18–23.4)	27.3 (11.3–99.4)	LC 100%, DC 80%, OS 90%	Endocrine G2 (2pts hypothyroidism, 3pts GH deficiency)
Mc Govern et al. ⁸⁴	2014	AT/RT	31	1.6	50.4 (9–54); 14 pts CSI (23.4–36)	24 (3–53)	Median OS 34.3mo, PFS 20.8mo	five pts imaging changes interpreted as RN
Weber et al. ⁹⁵	2015	AT/RT	15	1.4	54 all patients, no CSI	33.4 (9.7–69.2)	LF 20%, DBF 27%, SF 2%, 2y OS 64.6%, 2y PFS 66%	2y tox free survival 90%. No decrease of QoL after PT
Bishop et al. ⁹¹	2014	Craniopharyngioma	52 (21 PT)	8.9	50.4 (50.4–54)	59.6 (PT 33mo)	3y OS 96%, nodular FFS 96%, cystic FFS 76%. Same outcome for PT and IMRT	Endocrine G2 77%. No difference between PT and IMRT
MacDonald et al. ⁹⁷	2013	Ependymoma	70	3.2	55.8 (50.4–60)	46 (12–140.4)	3y LC 83%, PFS 76%, OS 95% 5y LC 77%, DC 83%	one pt hypothyroidism, two pts GH deficit, two pts hearing loss, two pts cavernoma. No drop in MI and OAS scores
Mizumoto et al. ⁹⁸	2015	Ependymoma	6	5	56.7 (50.4–61.2)	24.5 (13–44)	OS 100%, PFS 80%	one pt one-time seizure, one pt alopecia, no difficulty in daily life
Ares et al. ⁹²	2016	Ependymoma	50	2.6	59.4 (54–60)	43.4 (8.5–113.7)	5y LC 78%, OS 84%	38% G1/2, two pts G3 deafness, one pt G5 brainstem necrosis
Sato et al. ⁹⁹	2017	Ependymoma	79 (41 PT)	3.7	55.8 (50.4–59.4)	PT 31.2 (7.2–86.4) IMRT 58.8 (13.2–140.4)	3y OS 81% IMRT vs 97% PT ($p = .08$), PFS 60% IMRT vs 82% PT ($p = .0307$), Recurrence 55% IMRT vs 17% PT ($p = .005$)	Vascular disorder G2 + 10% (6 RN, one stroke, one cavernoma)
MacDonald et al. ⁹³	2011	Germ cell tumors	22	11	Total 44 (30.6–57.6) 1pt IF only seven pts WVRT 19.5–23.4 1pt WBRT 25.5 13 pts CSI 18.3–27	28 (13–97)	LC 100%, PFS 95%, OS 100%	two pts hypothyroidism, 2pts GH deficit. No new NC or auditory deficit
Hug et al. ⁹⁴	2002	Low grade glioma	27	8.7	55.2 (50.4–63)	39.6 (7.2–81.6)	LF 22%, OS 85%	Moya-Moya one pt
Greenberger et al. ⁷⁸	2014	Low grade glioma	32 (nine mix PT and photons)	11	52.2 (48.6–54)	91.2 (38.4–218.4)	6y PFS 89.7%, 8y PFS 82.8%, 8y OS 100%	Endocrine G2 > 80% at 10y (>40 Gy to pituitary and hypothalamus is RF), two pts G3 vasculopathy (Moya-Moya), age > 7y and hippocampus dose RF for NC decline, VA/VF decline four events, other visual tox nine events
Jimenez et al. ¹⁰⁰	2013	Medulloblastoma / supratentorial PNET	15	2.9	Total 54 (39.6–54) CSI 21.6 (18–30.6)	39 (3–102)	3y LF 7.7%, OS 85.6%	Orototoxicity nine pts (2 G3), Endocrine G2 three pts, significant height loss, NS if GH deficiency pts excluded, no loss from baseline IQ
Eaton et al. ¹⁰¹	2016	Medulloblastoma	88 (45 PT)	6	Total 54–55.8 CSI 23.4 (18–27)	74.4 PT pts 84 photon pts	6y PFS 78.8% PT vs 76.5% photon ($p = .948$). 6y OS 82% PT vs 87.6% photon ($p = .285$)	NR

(Continued)

Table 5 (Continued)

Author [ref]	year	Tumor type	# pts	Median Age [years]	Median Dose [GyRBE] (range)	Median FU [months] (range)	Outcome	Late Toxicity
Yock et al. ¹⁰²	2016	Medulloblastoma	59	6.6	Total 54 CSI 23.4 (23.4–36)	84 (62.4–98.4)	3y PFS 83%, OS 83% 5y PFS 80%, OS 83% 7y PFS 75%, OS 81%	Ototoxicity G3 + 12% at 3y and 16% at 5y and 7y; FSIQ decline by 1.5 point/y; Endocrine deficit 27%, 55 and 63% at 3, 5 and 7y; Cataract two pts, BS injury one pt, Stroke two pt

NS, not statistically significant; WBRT, whole brain radiotherapy; AT/RT, atypical teratoid/rhabdoid tumor; CSI, craniospinal irradiation; DBF, distant brain failure; DC, distant control; FFS, failure free survival; FSIQ, full scale intelligence quotient; FU, follow-up; G, toxicity grade; GH, growth hormone; GyRBE, Gray in relative biological effectiveness; IF, involved field; LC, local control; LF, local failure; MI, mean intelligence; NC, neurocognitive; NR, not reported; OAS, overall adaptive skills; OS, overall survival; PFS, progression free survival; RF, risk factor; RFS, recurrence free survival; RN, radiation necrosis; SF, spinal failure; PT, proton therapy; VA, visual acuity; VF, visual field; WVRT, whole ventricle radiotherapy; mo, months; pts, patients.

RBE were used across all seven studies. Grade 3–4 RN ranged between 2 and 3.6% at 5 years.^{82–88} PT has demonstrated its ability to better spare uninvolved normal tissues including critical OARs compared to standard photon therapy. It has therefore become a widely accepted radiation modality for several childhood malignancies. Advantages of PT for the irradiation of brain tumours reside in a better sparing of healthy brain tissue and other OARs (Figure 2), not limited but including the cochlea, the pituitary gland, the hippocampus, the optic structures and the brainstem.⁸⁹ For the spinal cord, posterior proton field arrangements (Figure 1b) allow for an excellent sparing of all organs anterior to the vertebral bodies as described above.⁹⁰ Pediatric brain tumours, for which PT has been most commonly used, are craniopharyngiomas,⁹¹ ependymomas (Figure 2),⁹² germ cell tumours,⁹³ low-grade gliomas,⁹⁴ medulloblastomas and atypical teratoid/rhabdoid tumours (ATRT)^{95,96} (Table 5). Four retrospective studies, published with exclusively ependymoma patients, reported OS and PFS rates ranging from 84–100% to 76–80%.^{92,97–99} In medulloblastoma studies,^{100,102,103} sample sizes ranged between 15 and 59 patients, with ages between 2.9 and 6.6 years. The context of re-irradiation also makes a particularly strong case for the use of very conformal RT modalities such as PT, as treatment of recurrences can still lead to cure in some instances, such as for localized ependymoma relapses.¹⁰¹

The administration of protons to children with brain tumors represent an unique opportunity to decrease the likelihood of late CNS toxicity by decreasing the integral dose to the brain, especially so in very young patients with tumors such as ATRTs, ependymomas or medulloblastomas.

Costs considerations/financial toxicity

Across HICs, cancer management costs are escalating, driven mainly by consumerism in health care, the demographic transition of a growing elderly population and by the delivery of costly new therapies. Although there is an association between high-spending health care systems and lower cancer mortality,¹⁰⁴ it is questionable if the growth in cancer spending is sustainable in the long-time in high-income countries.

Proton therapy is an expensive anti cancer treatment, with a cost factor of approximately 2.5, when compared to modern RT techniques.¹⁰⁵ This is certainly due to the considerable investment costs but also due to the high operation and maintenance costs. Ongoing technical developments may lead to cost reduction but it is not expected that a dramatic decrease in costs will be reached in the near future.¹⁰⁶ As a result, there is an ongoing debate on the value of proton therapy and its cost-effectiveness (CE).^{107,108}

As care for medical conditions, such as cancer, usually involves multiple disciplines and numerous interventions at different time-points, the true value cannot be determined by simply comparing costs of two treatment modalities. Consequently, CE analysis must also consider patient's longtime outcome, toxicity and quality of life by tracking patient outcomes and costs longitudinally.¹⁰⁹

Four publications on CE of proton therapy in brain tumours could be identified, of note all in pediatric cohorts (Table 6). All

Table 6. Cost-effectiveness studies for proton vs photon therapy of brain tumors

Author [ref]	year	Tumor type	Study design	Statistical Model Method	Included Parameters	Results
Lundkvist et al. ¹¹⁰	2005	Pediatric medulloblastoma	Comparison PBT vs IMRT	Markov cohort simulation model	Risk of hearing loss, IQ loss, GHD, hypothyroidism, osteoporosis, cardiac disease, fatal and nonfatal SMN	Gain of QALY of 0.68 per patient; Estimated cost difference (protons vs photons) per patient -23,646.5 EUR ICER of -34,622 EUR/QALY →Cost effective →Cost saving
Mailhot Vega et al. ¹¹¹	2013	Pediatric medulloblastoma	Comparison of PBT vs photon RT	Monte Carlo simulation	Risk of GHD, hearing loss, hypothyroidism, congestive heart failure coronary artery disease, ACTH deficiency, gonadotropin deficiency, SMN, death	Gain of QALY of 3.46; Total difference in costs (protons vs photons): - 32,579.1 Dollar ICER of -9,416 Dollar/QALY →Cost effective →Cost saving
Hirano et al. ¹¹²	2014	Pediatric medulloblastoma	Comparison of PBT vs IMRT	Markov cohort simulation model	Risk of hearing loss due to cochlear dose for three different QoL measures (EQ-5D, HUI3, SF-6D)	Gain of QALY between 0.98 and 1.82 and ICER of 11,773 and 21,716 Dollar/QALY dependent on QoL measure used →Cost effective
Mailhot Vega et al. ¹¹³	2015	Pediatric CNS tumors	Comparison of PBT vs photon RT in hypothalamic dose sparing	Markov cohort simulation model	Risk of GHD	Hypothalamic proton doses between 5 and 25 Gy can be cost-effective, between 5 and 20 Gy even cost saving in some scenarios

ACTH, adrenocorticotrophic hormone; GHD, growth hormone deficiency; ICER, incremental cost-effectiveness ratio; IMRT, intensity modulated radiation therapy; IQ, intelligence quotient; PBT, proton beam therapy; QoL, quality of life; QALY, quality adjusted life years; RT, radiation therapy; SMN, secondary malignant neoplasm.

used Markov modelling^{110,112,113} and Monte Carlo simulations¹¹¹ to compare proton vs photon therapy. All investigators have shown that proton therapy is cost-effective with regard to long-term risk of radiation side-effects. Three studies even demonstrated a cost saving effect of proton therapy.

These analyses are based on theoretical modelling concepts using assumptions, which remain questionable. Empirical comparative data establishing the clinical advantages and health economic appropriateness of proton compared to photon therapy is lacking but urgently needed. It is foreseen that costing data will be captured in the EORTC 1811 protocol/ParticleCare.

Most insurances reimburse the costs of proton therapy for brain tumours listed in this manuscript. Nevertheless, patients may experience expenses to cover costs for housing and traveling during 6–7 weeks treatment, special food and potentially lose wages. For some patients, these out of pocket payments can cause substantial financial distress that adversely affects a patient's quality of life, treatment choice, treatment compliance, and treatment outcome.¹¹⁴ Treatment related financial distress can be just as toxic as the effects of chemotherapy or radiation and

was therefore defined as a treatment related financial toxicity.¹¹⁵ Approximately 16% of patients undergoing proton therapy for brain tumours in Switzerland experience moderate to severe financial distress (unpublished own data). However, very limited evidence is available about the incidence of financial toxicity, its associated morbidity and its preventability in proton therapy.

CONCLUSIONS

The dose deposition advantage of PT for the treatment of brain tumours are instantly apparent when planning comparisons of proton vs photon are made. Evidence for PT in adult benign and low-grade tumours is however limited on retrospective analyses. The available data suggests that proton therapy achieves good local control in some high-grade tumours with acceptable toxicity and that the toxicity profile for low-grade tumours warrants prospective analyses. For skull-base, radio-resistant tumours, high-dose (*i.e.* >70 GyRBE) proton therapy, with non-stereotactic margins, have to be delivered to patients postoperatively. Delivering protons to children with brain tumours may increase the therapeutic ratio. In the era of EBM, high-quality data needs to be rapidly generated to justify the higher costing of this radiation modality, which can have substantial financial toxicity to the patients and their families.

REFERENCES

1. Palm RE, Oliver DE, Yang GQ, Abuodeh Y, Naghavi AO, Johnstone PAS. The role of dose escalation and proton therapy in perioperative or definitive treatment of chondrosarcoma and chordoma: an analysis of the National Cancer data base. *Cancer* 2019; **125**: 642–51. doi: <https://doi.org/10.1002/cncr.31958>

2. Weber DC, Ares C, Villa S, Peerdeman SM, Renard L, Baumert BG, et al. Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a phase-II parallel non-randomized and observation study (EORTC 22042-26042). *Radiother Oncol* 2018; **128**: 260–5. doi: <https://doi.org/10.1016/j.radonc.2018.06.018>
3. Indelicato DJ, Rotondo RL, Uezono H, Sandler ES, Aldana PR, Ranalli NJ, et al. Outcomes following proton therapy for pediatric low-grade glioma. *Int J Radiat Oncol Biol Phys* 2019;.
4. Sherman JC, Colvin MK, Mancuso SM, Batchelor TT, Oh KS, Loeffler JS, et al. Neurocognitive effects of proton radiation therapy in adults with low-grade glioma. *J Neurooncol* 2016; **126**: 157–64. doi: <https://doi.org/10.1007/s11060-015-1952-5>
5. Lomax AJ. Charged particle therapy: the physics of interaction. *Cancer J* 2009; **15**: 285–91. doi: <https://doi.org/10.1097/PPO.0b013e3181af5cc7>
6. Lomax A. Intensity modulation methods for proton radiotherapy. *Phys Med Biol* 1999; **44**: 185–205. doi: <https://doi.org/10.1088/0031-9155/44/1/014>
7. Lambrecht M, Eekers DBP, Alapetite C, Burnet NG, Calugaru V, Coremans IEM, et al. Radiation dose constraints for organs at risk in neuro-oncology; the European particle therapy Network consensus. *Radiother Oncol* 2018; **128**: 26–36. doi: <https://doi.org/10.1016/j.radonc.2018.05.001>
8. Vatner RE, Niemierko A, Misra M, Weyman EA, Goebel CP, Ebb DH, et al. Endocrine deficiency as a function of radiation dose to the hypothalamus and pituitary in pediatric and young adult patients with brain tumors. *JCO* 2018; **36**: 2854–62. doi: <https://doi.org/10.1200/JCO.2018.78.1492>
9. Zureick AH, Evans CL, Niemierko A, Grieco JA, Nichols AJ, Fullerton BC, et al. Left hippocampal dosimetry correlates with visual and verbal memory outcomes in survivors of pediatric brain tumors. *Cancer* 2018; **124**: 2238–45. doi: <https://doi.org/10.1002/cncr.31143>
10. Adeberg S, Harrabi S, Bougatf N, Verma V, Windisch P, Bernhardt D, et al. Dosimetric comparison of proton radiation therapy, volumetric modulated Arc therapy, and three-dimensional conformal radiotherapy based on intracranial tumor location. *Cancers* 2018; **10**: 401. doi: <https://doi.org/10.3390/cancers10110401>
11. Correia D, Terribilini D, Zepter S, Pica A, Bizzocchi N, Volken W, et al. Whole-ventricular irradiation for intracranial germ cell tumors: Dosimetric comparison of pencil beam scanned protons, intensity-modulated radiotherapy and volumetric-modulated Arc therapy. *Clin Transl Radiat Oncol* 2019; **15**: 53–61. doi: <https://doi.org/10.1016/j.ctro.2019.01.002>
12. El-Fayech C, Haddy N, Allodji RS, Veres C, Diop F, Kahlouche A, et al. Cerebrovascular diseases in childhood cancer survivors: role of the radiation dose to Willis circle arteries. *International Journal of Radiation Oncology*Biophysics* 2017; **97**: 278–86. doi: <https://doi.org/10.1016/j.ijrobp.2016.10.015>
13. Seravalli E, Bosman M, Lassen-Ramshad Y, Vestergaard A, Oldenburger F, Visser J, et al. Dosimetric comparison of five different techniques for craniospinal irradiation across 15 European centers: analysis on behalf of the SIOP-E-BTG (radiotherapy Working Group. *Acta Oncologica* 2018; **57**: 1240–9. doi: <https://doi.org/10.1080/0284186X.2018.1465588>
14. Tamura M, Sakurai H, Mizumoto M, Kamizawa S, Murayama S, Yamashita H, et al. Lifetime attributable risk of radiation-induced secondary cancer from proton beam therapy compared with that of intensity-modulated X-ray therapy in randomly sampled pediatric cancer patients. *J Radiat Res* 2017; **58**: 363–71. doi: <https://doi.org/10.1093/jrr/rrw088>
15. Miralbell R, Lomax A, Cella L, Schneider U. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. *International Journal of Radiation Oncology*Biophysics* 2002; **54**: 824–9. doi: [https://doi.org/10.1016/S0360-3016\(02\)02982-6](https://doi.org/10.1016/S0360-3016(02)02982-6)
16. Kahalley LS, Ris MD, Mahajan A, Okcu MF, Chintagumpala M, Paulino AC, et al. Prospective, longitudinal comparison of neurocognitive change in pediatric brain tumor patients treated with proton radiotherapy versus surgery only. *Neuro Oncol* 2019;07 Feb 2019. doi: <https://doi.org/10.1093/neuonc/noz041>
17. Verma V, Simone CB, Mishra MV. Quality of life and patient-reported outcomes following proton radiation therapy: a systematic review. *J Natl Cancer Inst* 2018; **110**: 341–53. doi: <https://doi.org/10.1093/jnci/djx208>
18. McGowan SE, Albertini F, Thomas SJ, Lomax AJ. Defining robustness protocols: a method to include and evaluate robustness in clinical plans. *Phys Med Biol* 2015; **60**: 2671–84. doi: <https://doi.org/10.1088/0031-9155/60/7/2671>
19. Unkelbach J, Alber M, Bangert M, Bokrantz R, Chan TCY, Deasy JO, et al. Robust radiotherapy planning. *Phys Med Biol* 2018; **63**: 22TR02. doi: <https://doi.org/10.1088/1361-6560/aae659>
20. Paganetti H. Relative biological effectiveness (RBE) values for proton beam therapy: variations as a function of biological endpoint, dose, and linear energy transfer. *Phys Med Biol* 2014; **59**: R419–R472. doi: <https://doi.org/10.1088/0031-9155/59/22/R419>
21. Lühr A, von Neubeck C, Krause M, Troost EGC. Relative biological effectiveness in proton beam therapy - Current knowledge and future challenges. *Clin Transl Radiat Oncol* 2018; **9**: 35–41. doi: <https://doi.org/10.1016/j.ctro.2018.01.006>
22. Unkelbach J, Botas P, Giantsoudi D, Gorissen BL, Paganetti H. Reoptimization of intensity modulated proton therapy plans based on linear energy transfer. *International Journal of Radiation Oncology*Biophysics* 2016; **96**: 1097–106. doi: <https://doi.org/10.1016/j.ijrobp.2016.08.038>
23. Lühr A, von Neubeck C, Pawelke J, Seidlitz A, Peitzsch C, Bentzen SM, et al. "Radiobiology of Proton Therapy": Results of an international expert workshop. *Radiother Oncol* 2018; **128**: 56–67. doi: <https://doi.org/10.1016/j.radonc.2018.05.018>
24. Peeler CR, Mirkovic D, Titt U, Blanchard P, Gunther JR, Mahajan A, et al. Clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma. *Radiother Oncol* 2016; **121**: 395–401. doi: <https://doi.org/10.1016/j.radonc.2016.11.001>
25. Haas-Kogan D, Indelicato D, Paganetti H, Esiasvili N, Mahajan A, Yock T, et al. National Cancer Institute workshop on proton therapy for children: considerations regarding brainstem injury. *International Journal of Radiation Oncology*Biophysics* 2018; **101**: 152–68. doi: <https://doi.org/10.1016/j.ijrobp.2018.01.013>
26. Fjæra LF, Li Z, Ytre-Hauge KS, Muren LP, Indelicato DJ, Lassen-Ramshad Y, et al. Linear energy transfer distributions in the brainstem depending on tumour location in intensity-modulated proton therapy of paediatric cancer. *Acta Oncol* 2017; **56**: 763–8. doi: <https://doi.org/10.1080/0284186X.2017.1314007>
27. Grau C, Baumann M, Weber DC. Optimizing clinical research and generating prospective high-quality data in particle therapy in Europe: introducing the European particle therapy Network (EPTN). *Radiother Oncol* 2018; **128**: 1–3. doi: <https://doi.org/10.1016/j.radonc.2018.06.021>

28. Cox JD. Impediments to comparative clinical trials with proton therapy. *International Journal of Radiation Oncology*Biophysics* 2016; **95**: 4–8. doi: <https://doi.org/10.1016/j.ijrobp.2015.09.036>
29. Goitein M. Trials and tribulations in charged particle radiotherapy. *Radiother Oncol* 2010; **95**: 23–31. doi: <https://doi.org/10.1016/j.radonc.2009.06.012>
30. Langendijk JA, Boersma LJ, Rasch CRN, van Vulpen M, Reitsma JB, van der Schaaf A, et al. Clinical trial strategies to compare protons with photons. *Semin Radiat Oncol* 2018; **28**: 79–87. doi: <https://doi.org/10.1016/j.semradonc.2017.11.008>
31. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med* 2016; **374**: 1344–55. doi: <https://doi.org/10.1056/NEJMoa1500925>
32. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol* 2009; **8**: 810–8. doi: [https://doi.org/10.1016/S1474-4422\(09\)70204-2](https://doi.org/10.1016/S1474-4422(09)70204-2)
33. Eekers DBP, Roelofs E, Cubillos-Mesías M, Niël C, Smeenk RJ, Hoebein A, et al. Intensity-modulated proton therapy decreases dose to organs at risk in low-grade glioma patients: results of a multicentric *in silico* ROCOCO trial. *Acta Oncol* 2019; **58**: 57–65. doi: <https://doi.org/10.1080/0284186X.2018.1529424>
34. Shih HA, Sherman JC, Nachtigall LB, Colvin MK, Fullerton BC, Daartz J, et al. Proton therapy for low-grade gliomas: results from a prospective trial. *Cancer* 2015; **121**: 1712–9. doi: <https://doi.org/10.1002/cncr.29237>
35. Hauswald H, Rieken S, Ecker S, Kessel KA, Herfarth K, Debus J, et al. First experiences in treatment of low-grade glioma grade I and II with proton therapy. *Radiat Oncol* 2012; **7**: 189. doi: <https://doi.org/10.1186/1748-717X-7-189>
36. Badiyan SN, Ulmer S, Ahlhelm FJ, Fredh ASM, Kliebsch U, Calaminus G, et al. Clinical and radiologic outcomes in adults and children treated with Pencil-Beam scanning proton therapy for low-grade glioma. *International Journal of Particle Therapy* 2017; **3**: 450–60. doi: <https://doi.org/10.14338/IJPT-16-00031.1>
37. Fitzek MM, Thornton AF, Harsh G, Rabinov JD, Munzenrider JE, Lev M, et al. Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: results of an institutional phase II/II trial. *International Journal of Radiation Oncology*Biophysics* 2001; **51**: 131–7. doi: [https://doi.org/10.1016/S0360-3016\(01\)01589-9](https://doi.org/10.1016/S0360-3016(01)01589-9)
38. McDonald MW, Plankenhorn DA, McMullen KP, Henderson MA, Dropcho EJ, Shah MV, et al. Proton therapy for atypical meningiomas. *J Neurooncol* 2015; **123**: 123–8. doi: <https://doi.org/10.1007/s11060-015-1770-9>
39. Halasz LM, Bussière MR, Dennis ER, Niemierko A, Chapman PH, Loeffler JS, et al. Proton stereotactic radiosurgery for the treatment of benign meningiomas. *International Journal of Radiation Oncology*Biophysics* 2011; **81**: 1428–35. doi: <https://doi.org/10.1016/j.ijrobp.2010.07.1991>
40. Weber DC, Schneider R, Goitein G, Koch T, Ares C, Geismar JH, et al. Spot scanning-based proton therapy for intracranial meningioma: long-term results from the Paul Scherrer Institute. *International Journal of Radiation Oncology*Biophysics* 2012; **83**: 865–71. doi: <https://doi.org/10.1016/j.ijrobp.2011.08.027>
41. Slater JD, Loreda LN, Chung A, Bush DA, Patyal B, Johnson WD, et al. Fractionated proton radiotherapy for benign cavernous sinus meningiomas. *International Journal of Radiation Oncology*Biophysics* 2012; **83**: e633–7. doi: <https://doi.org/10.1016/j.ijrobp.2012.01.079>
42. Combs SE, Welzel T, Habermehl D, Rieken S, Dittmar J-O, Kessel K, et al. Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and 68Ga-DOTATOC-PET. *Acta Oncol* 2013; **52**: 514–20. doi: <https://doi.org/10.3109/0284186X.2013.762996>
43. Vlachogiannis P, Gudjonsson O, Montelius A, Grusell E, Isacson U, Nilsson K, et al. Hypofractionated high-energy proton-beam irradiation is an alternative treatment for WHO grade I meningiomas. *Acta Neurochir* 2017; **159**: 2391–400. doi: <https://doi.org/10.1007/s00701-017-3352-4>
44. Murray FR, Snider JW, Bolsi A, Lomax AJ, Walser M, Kliebsch U, et al. Long-term clinical outcomes of pencil beam scanning proton therapy for benign and non-benign intracranial meningiomas. *International Journal of Radiation Oncology*Biophysics* 2017; **99**: 1190–8. doi: <https://doi.org/10.1016/j.ijrobp.2017.08.005>
45. El Shafie RA, Czech M, Kessel KA, Habermehl D, Weber D, Rieken S, et al. Clinical outcome after particle therapy for meningiomas of the skull base: toxicity and local control in patients treated with active rasterscanning. *Radiat Oncol* 2018; **13**: 54. doi: <https://doi.org/10.1186/s13014-018-1002-5>
46. Smoll NR, Gautschi OP, Radovanovic I, Schaller K, Weber DC. Incidence and relative survival of chordomas: the standardized mortality ratio and the impact of chordomas on a population. *Cancer* 2013; **119**: 2029–37. doi: <https://doi.org/10.1002/cncr.28032>
47. Pearlman AW, Friedman M. Radical radiation therapy of chordoma. *American Journal of Roentgenology* 1970; **108**: 333–41. doi: <https://doi.org/10.2214/ajr.108.2.333>
48. Rich TA, Schiller A, Suit HD, Mankin HJ. Clinical and pathologic review of 48 cases of chordoma. *Cancer* 1985; **56**: 182–7. doi: [https://doi.org/10.1002/1097-0142\(19850701\)56:1<182::AID-CNCR2820560131>3.0.CO;2-J](https://doi.org/10.1002/1097-0142(19850701)56:1<182::AID-CNCR2820560131>3.0.CO;2-J)
49. Debus J, Hug EB, Liebsch NJ, O'Farrell D, Finkelstein D, Efrid J, et al. Brainstem tolerance to conformal radiotherapy of skull base tumors. *International Journal of Radiation Oncology*Biophysics* 1997; **39**: 967–75. doi: [https://doi.org/10.1016/S0360-3016\(97\)00364-7](https://doi.org/10.1016/S0360-3016(97)00364-7)
50. Weber DC, Murray F, Combescure C, Calugaru V, Alapetite C, Albertini F, et al. Long term outcome of skull-base chondrosarcoma patients treated with high-dose proton therapy with or without conventional radiation therapy. *Radiother Oncol* 2018; **129**: 520–6. doi: <https://doi.org/10.1016/j.radonc.2018.06.040>
51. Weber DC, Malyapa R, Albertini F, Bolsi A, Kliebsch U, Walser M, et al. Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy. *Radiother Oncol* 2016; **120**: 169–74. doi: <https://doi.org/10.1016/j.radonc.2016.05.011>
52. Hug EB, Loreda LN, Slater JD, DeVries A, Grove RI, Schaefer RA, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 1999; **91**: 432–9. doi: <https://doi.org/10.3171/jns.1999.91.3.0432>
53. Fung V, Calugaru V, Bolle S, Mammar H, Alapetite C, Maingon P, et al. Proton beam therapy for skull base chordomas in 106 patients: a dose adaptive radiation protocol. *Radiother Oncol* 2018; **128**: 198–202. doi: <https://doi.org/10.1016/j.radonc.2017.12.017>
54. Takagi M, Demizu Y, Nagano F, Terashima K, Fujii O, Jin D, et al. Treatment outcomes of proton or carbon ion therapy for skull base chordoma: a retrospective study. *Radiat*

- Oncol* 2018; **13**: 232. doi: <https://doi.org/10.1186/s13014-018-1173-0>
55. Romero J, Cardenes H, la Torre A, Valcarcel F, Magallon R, Regueiro C, et al. Chordoma: results of radiation therapy in eighteen patients. *Radiother Oncol* 1993; **29**: 27–32. doi: [https://doi.org/10.1016/0167-8140\(93\)90169-9](https://doi.org/10.1016/0167-8140(93)90169-9)
 56. Catton C, O'Sullivan B, Bell R, Laperriere N, Cummings B, Fornasier V, et al. Chordoma: long-term follow-up after radical photon irradiation. *Radiother Oncol* 1996; **41**: 67–72. doi: [https://doi.org/10.1016/S0167-8140\(96\)01805-1](https://doi.org/10.1016/S0167-8140(96)01805-1)
 57. Choy W, Terterov S, Ung N, Kaprelian T, Trang A, DeSalles A, et al. Adjuvant stereotactic radiosurgery and radiation therapy for the treatment of intracranial chordomas. *J Neurol Surg B Skull Base* 2016; **77**: 038–46. doi: <https://doi.org/10.1055/s-0035-1554907>
 58. Zakaria WK, Hafez RF, Taha AN. Gamma knife management of skull base chordomas: is it a choice? *Asian J Neurosurg* 2018; **13**: 1037–41. doi: https://doi.org/10.4103/ajns.AJNS_61_17
 59. Zorlu F, Gultekin M, Cengiz M, Yildiz F, Akyol F, Gurkaynak M, et al. Fractionated stereotactic radiosurgery treatment results for skull base chordomas. *Technol Cancer Res Treat* 2014; **13**: 11–19. doi: <https://doi.org/10.7785/tcrt.2012.500354>
 60. Snider JW, Schneider RA, Poelma-Tap D, Stieb S, Murray FR, Placidi L, et al. Long-term outcomes and prognostic factors after Pencil-Beam scanning proton radiation therapy for spinal chordomas: a large, single-institution cohort. *International Journal of Radiation Oncology*Biophysics* 2018; **101**: 226–33. doi: <https://doi.org/10.1016/j.ijrobp.2018.01.060>
 61. Youn SH, Cho KH, Kim J-Y, Ha B, Lim YK, Jeong JH, et al. Clinical outcome of proton therapy for patients with chordomas. *Radiat Oncol J* 2018; **36**: 182–91. doi: <https://doi.org/10.3857/roj.2018.00164>
 62. Hayashi Y, Mizumoto M, Akutsu H, Takano S, Matsumura A, Okumura T, et al. Hyperfractionated high-dose proton beam radiotherapy for clival chordomas after surgical removal. *Br J Radiol* 2016; **89**: 20151051. doi: <https://doi.org/10.1259/bjr.20151051>
 63. Gatfield ER, Noble DJ, Barnett GC, Early NY, Hoole ACF, Kirkby NF, et al. Tumour volume and dose influence outcome after surgery and high-dose photon radiotherapy for chordoma and chondrosarcoma of the skull base and spine. *Clin Oncol* 2018; **30**: 243–53. doi: <https://doi.org/10.1016/j.clon.2018.01.002>
 64. Demizu Y, Mizumoto M, Onoe T, Nakamura N, Kikuchi Y, Shibata T, et al. Proton beam therapy for bone sarcomas of the skull base and spine: a retrospective nationwide multicenter study in Japan. *Cancer Sci* 2017; **108**: 972–7. doi: <https://doi.org/10.1111/cas.13192>
 65. Feuvret L, Bracci S, Calugaru V, Bolle S, Mammar H, De Marzi L, et al. Efficacy and safety of adjuvant proton therapy combined with surgery for chondrosarcoma of the skull base: a retrospective, population-based study. *International Journal of Radiation Oncology*Biophysics* 2016; **95**: 312–21. doi: <https://doi.org/10.1016/j.ijrobp.2015.12.016>
 66. Deraniyagala R, Yeung D, Mendenhall W, Li Z, Morris C, Mendenhall N, et al. Proton therapy for skull base chordomas: an outcome study from the University of Florida proton therapy Institute. *J Neurol Surg B Skull Base* 2014; **75**: 053–7. doi: <https://doi.org/10.1055/s-0033-1354579>
 67. Yasuda M, Bresson D, Chibbaro S, Cornelius JF, Polivka M, Feuvret L, et al. Chordomas of the skull base and cervical spine: clinical outcomes associated with a multimodal surgical resection combined with proton-beam radiation in 40 patients. *Neurosurg Rev* 2012; **35**: 171–83discussion 82–3. doi: <https://doi.org/10.1007/s10143-011-0334-5>
 68. Fuji H, Nakasu Y, Ishida Y, Horiguchi S, Mitsuya K, Kashiwagi H, et al. Feasibility of proton beam therapy for chordoma and chondrosarcoma of the skull base. *Skull Base* 2011; **21**: 201–6. doi: <https://doi.org/10.1055/s-0031-1275636>
 69. Noël G, Habrand J-L, Mammar H, Pontvert D, Haie-Méder C, Hasboun D, et al. Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protonthérapie D'Orsay experience. *International Journal of Radiation Oncology*Biophysics* 2001; **51**: 392–8. doi: [https://doi.org/10.1016/S0360-3016\(01\)01634-0](https://doi.org/10.1016/S0360-3016(01)01634-0)
 70. Terahara A, Niemierko A, Goitein M, Finkelstein D, Hug E, Liebsch N, et al. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. *International Journal of Radiation Oncology*Biophysics* 1999; **45**: 351–8. doi: [https://doi.org/10.1016/S0360-3016\(99\)00146-7](https://doi.org/10.1016/S0360-3016(99)00146-7)
 71. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. *Strahlenther Onkol* 1999; **175** Suppl 2(Suppl 2): 57–63. doi: <https://doi.org/10.1007/BF03038890>
 72. Austin-Seymour M, Munzenrider J, Goitein M, Verhey L, Urie M, Gentry R, et al. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. *J Neurosurg* 1989; **70**: 13–17. doi: <https://doi.org/10.3171/jns.1989.70.1.0013>
 73. Berson AM, Castro JR, Petti P, Phillips TL, Gauger GE, Gutin P, et al. Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: the Lawrence Berkeley laboratory experience. *International Journal of Radiation Oncology*Biophysics* 1988; **15**: 559–65. doi: [https://doi.org/10.1016/0360-3016\(88\)90295-7](https://doi.org/10.1016/0360-3016(88)90295-7)
 74. Pehlivan B, Ares C, Lomax AJ, Stadelmann O, Goitein G, Timmermann B, et al. Temporal lobe toxicity analysis after proton radiation therapy for skull base tumors. *International Journal of Radiation Oncology*Biophysics* 2012; **83**: 1432–40. doi: <https://doi.org/10.1016/j.ijrobp.2011.10.042>
 75. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol* 2017; **18**: 719–31. doi: [https://doi.org/10.1016/S1470-2045\(17\)30186-9](https://doi.org/10.1016/S1470-2045(17)30186-9)
 76. Pui C-H, Pei D, Pappo AS, Howard SC, Cheng C, Sandlund JT, et al. Treatment outcomes in black and white children with cancer: results from the SEER database and ST Jude Children's Research Hospital, 1992 through 2007. *JCO* 2012; **30**: 2005–12. doi: <https://doi.org/10.1200/JCO.2011.40.8617>
 77. Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, et al. The cumulative burden of surviving childhood cancer: an initial report from the ST Jude lifetime cohort Study (SJLIFE). *The Lancet* 2017; **390**: 2569–82. doi: [https://doi.org/10.1016/S0140-6736\(17\)31610-0](https://doi.org/10.1016/S0140-6736(17)31610-0)
 78. Greenberger BA, Pulsifer MB, Ebb DH, MacDonald SM, Jones RM, Butler WE, et al. Clinical outcomes and late Endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas. *International Journal of Radiation Oncology*Biophysics* 2014; **89**: 1060–8. doi: <https://doi.org/10.1016/j.ijrobp.2014.04.053>
 79. Moeller BJ, Chintagumpala M, Philip JJ, Grosshans DR, McAleer MF, Woo SY, et al. Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy. *Radiat Oncol* 2011; **6**: 58. doi: <https://doi.org/10.1186/1748-717X-6-58>

80. Krasin MJ, Constone LS, Friedman DL, Marks LB. Radiation-related treatment effects across the age spectrum: differences and similarities or what the old and young can learn from each other. *Semin Radiat Oncol* 2010; **20**: 21–9. doi: <https://doi.org/10.1016/j.semradonc.2009.09.001>
81. Plimpton SR, Stence N, Hemenway M, Hankinson TC, Foreman N, Liu AK. Cerebral radiation necrosis in pediatric patients. *Pediatr Hematol Oncol* 2015; **32**: 78–83. doi: <https://doi.org/10.3109/08880018.2013.791738>
82. Sabin ND, Merchant TE, Harreld JH, Patay Z, Klimo P, Qaddoumi I, et al. Imaging changes in very young children with brain tumors treated with proton therapy and chemotherapy. *AJNR Am J Neuroradiol* 2013; **34**: 446–50. doi: <https://doi.org/10.3174/ajnr.A3219>
83. Indelicato DJ, Flampouri S, Rotondo RL, Bradley JA, Morris CG, Aldana PR, et al. Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy. *Acta Oncol* 2014; **53**: 1298–304. doi: <https://doi.org/10.3109/0284186X.2014.957414>
84. McGovern SL, Okcu MF, Munsell ME, Kumbalasseriyl N, Grosshans DR, McAleer ME, et al. Outcomes and acute toxicities of proton therapy for pediatric atypical teratoid/rhabdoid tumor of the central nervous system. *International Journal of Radiation Oncology*Biophysics* 2014; **90**: 1143–52. doi: <https://doi.org/10.1016/j.ijrobp.2014.08.354>
85. Gunther JR, Sato M, Chintagumpala M, Ketonen L, Jones JY, Allen PK, et al. Imaging changes in pediatric intracranial ependymoma patients treated with proton beam radiation therapy compared to intensity modulated radiation therapy. *International Journal of Radiation Oncology*Biophysics* 2015; **93**: 54–63. doi: <https://doi.org/10.1016/j.ijrobp.2015.05.018>
86. Giantsoudi D, Sethi RV, Yeap BY, Eaton BR, Ebb DH, Caruso PA, et al. Incidence of CNS injury for a cohort of 111 patients treated with proton therapy for medulloblastoma: let and RBE associations for areas of injury. *International Journal of Radiation Oncology*Biophysics* 2016; **95**: 287–96. doi: <https://doi.org/10.1016/j.ijrobp.2015.09.015>
87. Bojaxhiu B, Ahlhelm F, Walser M, Placidi L, Kliebsch U, Mikroutsikos L, et al. Radiation Necrosis and White Matter Lesions in Pediatric Patients With Brain Tumors Treated With Pencil Beam Scanning Proton Therapy. *International Journal of Radiation Oncology*Biophysics* 2018; **100**: 987–96. doi: <https://doi.org/10.1016/j.ijrobp.2017.11.037>
88. Gentile MS, Yeap BY, Paganetti H, Goebel CP, Gaudet DE, Gallotto SL, et al. Brainstem injury in pediatric patients with posterior fossa tumors treated with proton beam therapy and associated Dosimetric factors. *International Journal of Radiation Oncology*Biophysics* 2018; **100**: 719–29. doi: <https://doi.org/10.1016/j.ijrobp.2017.11.026>
89. Merchant TE, Hua C-H, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer* 2008; **51**: 110–7. doi: <https://doi.org/10.1002/pbc.21530>
90. St. Clair WH, Adams JA, Bues M, Fullerton BC, La Shell S, Kooy HM, et al. Advantage of protons compared to conventional x-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *International Journal of Radiation Oncology*Biophysics* 2004; **58**: 727–34. doi: [https://doi.org/10.1016/S0360-3016\(03\)01574-8](https://doi.org/10.1016/S0360-3016(03)01574-8)
91. Bishop AJ, Greenfield B, Mahajan A, Paulino AC, Okcu MF, Allen PK, et al. Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. *International Journal of Radiation Oncology*Biophysics* 2014; **90**: 354–61. doi: <https://doi.org/10.1016/j.ijrobp.2014.05.051>
92. Ares C, Albertini F, Frei-Welte M, Bolsi A, Grotzer MA, Goitein G, et al. Pencil beam scanning proton therapy for pediatric intracranial ependymoma. *J Neurooncol* 2016; **128**: 137–45. doi: <https://doi.org/10.1007/s11060-016-2090-4>
93. MacDonald SM, Trofimov A, Safai S, Adams J, Fullerton B, Ebb D, et al. Proton radiotherapy for pediatric central nervous system germ cell tumors: early clinical outcomes. *International Journal of Radiation Oncology*Biophysics* 2011; **79**: 121–9. doi: <https://doi.org/10.1016/j.ijrobp.2009.10.069>
94. Hug EB, Muenster MW, Archambeau JO, DeVries A, Liwnicz B, Loredi LN, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. *Strahlenther Onkol* 2002; **178**: 10–17. doi: <https://doi.org/10.1007/s00066-002-0874-2>
95. Weber DC, Ares C, Malyapa R, Albertini F, Calaminus G, Kliebsch U, et al. Tumor control and QOL outcomes of very young children with atypical teratoid/rhabdoid tumor treated with focal only chemo-radiation therapy using pencil beam scanning proton therapy. *J Neurooncol* 2015; **121**: 389–97. doi: <https://doi.org/10.1007/s11060-014-1648-2>
96. De Amorim Bernstein K, Sethi R, Trofimov A, Zeng C, Fullerton B, Yeap BY, et al. Early clinical outcomes using proton radiation for children with central nervous system atypical teratoid rhabdoid tumors. *International Journal of Radiation Oncology*Biophysics* 2013; **86**: 114–20. doi: <https://doi.org/10.1016/j.ijrobp.2012.12.004>
97. MacDonald SM, Safai S, Trofimov A, Wolfgang J, Fullerton B, Yeap BY, et al. Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. *International Journal of Radiation Oncology*Biophysics* 2008; **71**: 979–86. doi: <https://doi.org/10.1016/j.ijrobp.2007.11.065>
98. Mizumoto M, Oshiro Y, Takizawa D, Fukushima T, Fukushima H, Yamamoto T, et al. Proton beam therapy for pediatric ependymoma. *Pediatr Int* 2015; **57**: 567–71. doi: <https://doi.org/10.1111/ped.12624>
99. Sato M, Gunther JR, Mahajan A, Jo E, Paulino AC, Adesina AM, et al. Progression-free survival of children with localized ependymoma treated with intensity-modulated radiation therapy or proton-beam radiation therapy. *Cancer* 2017; **123**: 2570–8. doi: <https://doi.org/10.1002/cncr.30623>
100. Jimenez RB, Sethi R, Depauw N, Pulsifer MB, Adams J, McBride SM, et al. Proton radiation therapy for pediatric medulloblastoma and supratentorial primitive neuroectodermal tumors: outcomes for very young children treated with upfront chemotherapy. *International Journal of Radiation Oncology*Biophysics* 2013; **87**: 120–6. doi: <https://doi.org/10.1016/j.ijrobp.2013.05.017>
101. Eaton BR, Chowdhry V, Weaver K, Liu L, Ebb D, MacDonald SM, et al. Use of proton therapy for re-irradiation in pediatric intracranial ependymoma. *Radiother Oncol* 2015; **116**: 301–8. doi: <https://doi.org/10.1016/j.radonc.2015.07.023>
102. Yock TI, Yeap BY, Ebb DH, Weyman E, Eaton BR, Sherry NA, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. *Lancet Oncol* 2016; **17**: 287–98. doi: [https://doi.org/10.1016/S1470-2045\(15\)00167-9](https://doi.org/10.1016/S1470-2045(15)00167-9)
103. Eaton BR, Esiashvili N, Kim S, Patterson B, Weyman EA, Thornton LT, et al.

- Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. *Neuro Oncol* 2016; **18**: 881–7. doi: <https://doi.org/10.1093/neuonc/nov302>
104. Stevens W, Philipson TJ, Khan ZM, MacEwan JP, Linthicum MT, Goldman DP. Cancer mortality reductions were greatest among countries where cancer care spending rose the most, 1995–2007. *Health Aff* 2015; **34**: 562–70. doi: <https://doi.org/10.1377/hlthaff.2014.0634>
 105. Goitein M, Jermann M. The relative costs of proton and X-ray radiation therapy. *Clin Oncol* 2003; **15**: S37–S50. doi: <https://doi.org/10.1053/clon.2002.0174>
 106. Schippers JM, Lomax A, Garonna A, Parodi K. Can technological improvements reduce the cost of proton radiation therapy? *Semin Radiat Oncol* 2018; **28**: 150–9. doi: <https://doi.org/10.1016/j.semradonc.2017.11.007>
 107. Verma V, Mishra MV, Mehta MP. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. *Cancer* 2016; **122**: 1483–501. doi: <https://doi.org/10.1002/cncr.29882>
 108. Lievens Y, Pijls-Johannesma M. Health economic controversy and cost-effectiveness of proton therapy. *Semin Radiat Oncol* 2013; **23**: 134–41. doi: <https://doi.org/10.1016/j.semradonc.2012.11.005>
 109. Porter ME. What is value in health care? *N Engl J Med* 2010; **363**: 2477–81. doi: <https://doi.org/10.1056/NEJMp1011024>
 110. Lundkvist J, Ekman M, Ericsson SR, Jönsson B, Glimelius B. Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. *Cancer* 2005; **103**: 793–801. doi: <https://doi.org/10.1002/cncr.20844>
 111. Mailhot Vega RB, Kim J, Bussière M, Hattangadi J, Hollander A, Michalski J, et al. Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer* 2013; **119**: 4299–307. doi: <https://doi.org/10.1002/cncr.28322>
 112. Hirano E, Fuji H, Onoe T, Kumar V, Shirato H, Kawabuchi K. Cost-effectiveness analysis of cochlear dose reduction by proton beam therapy for medulloblastoma in childhood. *J Radiat Res* 2014; **55**: 320–7. doi: <https://doi.org/10.1093/jrr/rrt112>
 113. Mailhot Vega R, Kim J, Hollander A, Hattangadi-Gluth J, Michalski J, Tarbell NJ, et al. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer* 2015; **121**: 1694–702. doi: <https://doi.org/10.1002/cncr.29209>
 114. Zafar SY. Financial toxicity of cancer care: it's time to intervene. *J Natl Cancer Inst* 2016; **108**: 12. doi: <https://doi.org/10.1093/jnci/djv370>
 115. Zafar SY, Peppercorn JM, Schrag D, Taylor DH, Goetzinger AM, Zhong X, et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *Oncologist* 2013; **18**: 381–90. doi: <https://doi.org/10.1634/theoncologist.2012-0279>